REMARKS

I. Status of the Claims and Amendments

After entering this amendment, claims 1-12, 14 and 19-22 will be pending in this application. Applicants acknowledge the Examiner's rejoinder of claims 12 and 19. Claims 2 and 19 are amended herein to be independent claims, and claim 4 is amended to remove a repetitive phrase. No new matter has been added by these amendments. Claim 18 has been cancelled without prejudice or disclaimer. Claims 20-22 have been withdrawn by the Examiner for being directed to non-elected subject matter.

Applicants would like thank the Examiner for her time during the two telephonic interviews of December 18, 2008. Applicants acknowledge that the outstanding Office Action is non-final, and agree with the Examiner's Interview Summary.

II. Claim Objections

The Examiner objects to claim 4 due to the repeated proviso. Office Action at 2. Applicants amended claim 4 to delete the repeated text. Thus, Applicants request withdrawal of the objection.

The Examiner objects to claims 5 and 8-11 for "being dependent upon a rejected base claim." Office Action at page 4. In view of the remarks made below with regards to claim 1, from which claims 5 and 8-11 ultimately depend, Applicants believe that claim 1 is in condition for allowance, and therefore, claims 5 and 8-11 are also allowable. Accordingly, Applicants respectfully request that this objection be withdrawn.

Lastly, claims 18 and 20-22 are objected to "as drawn to an invention nonelected with traverse." Office Action at 3. Applicants respectfully disagree with the Examiner, and continue to request rejoinder of claims 20-22 for the reasons of record, at least

because the examination of the withdrawn claims in this application would not represent an undue burden and would not require an additional search.

III. Rejections under § 112

A. Second paragraph

The Examiner rejects claims 1-4, 6, 7, 12, 14, and 19 under 35 U.S.C. § 112, second paragraph as being allegedly "indefinite." Office Action at 4. Specifically, the Examiner takes issue with the term "alkylene groups" in claims 1 and 4, and states that "R_3 is defined as an aryl or heteroaryl and alkylene is CH_2, which is divalent" and "[t]hus, claims 1-4, 6, 7, 12, 14, and 19 are vague." *Id.* Applicants respectfully disagree and traverse the rejection.

R_3 is defined in claims 1-4, 6, 7, 12, 14, and 19, as the following formula:

$$—(CH_2)_n—G$$

The variable G, within the definition of R_3, can be a "monocyclic or bicyclic aryl or heteroaryl group comprising from zero to four heteroatoms which group is optionally substituted by one or more substituents . . . ." *See e.g.,* claim 1. Thus, R_3 is not defined in the claims as "an aryl or heteroaryl," although the variable G, within the context of R_3, may be chosen from an aryl and heteroaryl. Thus, Applicants submit that the definition of R_3 is clear and definite. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner further rejects claim 2, for lack of antecedent basis for the term "a cycloalkyl group" as a substituent for R_1 or R_2 and "a hydroxyl group" as a substituent for "R_1 and R_2 combined." Office Action at 4. Although Applicants disagree with the

rejection, Applicants have amended claim 2 to be an independent claim. Support for the term "a cycloalkyl group" as a substituent for R_1 or R_2 in claim 2, is fully supported in the specification, for example, at page 23, ll. 1-4, thus providing sufficient support for the term "a cycloalkyl group" as a substituent for R_1 and R_2 combined.

Further, support for the term "a hydroxyl group" as a substituent for R_1 and R_2 combined, is supported in the specification, for example, at page 23. ll. 5-10, thus providing sufficient support for the term "a hydroxyl group" as a substituent for R_1 or R_2 combined. For at least these reasons, Applicants respectfully request that this rejection be withdrawn.

B. First paragraph

The Examiner rejects claim 19 under 35 U.S.C. § 112, first paragraph, "as failing to comply with enablement requirement." Office Action at 4. The Examiner contends that "[t]he claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains." *Id.* Applicants respectfully traverse this rejection.

1. The specification, in light of the knowledge in the art, properly enables the claimed invention

Applicants have presented evidence that the compounds of the invention are effective PDE7 inhibitors. *See, e.g.*, specification at p. 28-29. For example, the specification discloses that "[u]sing the assay described above [to determine PDE7 inhibition,] the IC_{50} of all compounds in the examples was determined to be smaller than 10 micromolar." *Id.* at 28, lines 29-30. A low value for the half maximal inhibitory concentration (IC_{50}) is desired because it indicates that less concentration of the test

compound is needed to inhibit the PDE7 activity by half. Not only does the specification teach that the compounds of the invention have in general an IC_{50} of less than 10 μM, but also discloses numerous specific compounds that have higher inhibitory potency by displaying an IC_{50} of less than 1 μM. *Id.* at 28, lines 30-32.

The Examiner refers to the lack of *in vivo* working examples for PDE7 inhibition and the treatment of the diseases recited in claim 19 as evidence of non-enablement. However, it is well established that the type of *in vitro* studies described in the specification may be sufficient to satisfy §112, even in the absence of *in vivo* studies. For example, the M.P.E.P. cites *In re Brana* (51 F.3d 1560 (Fed. Cir. 1995)) as an example where the Federal Circuit ruled that *in vitro* data did support *in vivo* applications. M.P.E.P. §2164.02, under Correlation: *In Vitro/In Vivo.*

The Examiner argues that the diseases recited in claim 19 "cannot be treated generally with one drug" and that they "are all different diseases and disorders, which occur at different locations and by different modes of action in the body." Office Action at 8. The Examiner also presented a long list of different cancers that in her opinion fell within the scope of treatment of claim 19 (Office Action at 6-7), and then stated that "no one has been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers." *Id.* at 9. These statements by the Examiner, however, ignore an explicit limitation in the claims explaining that to the type of pathological conditions or diseases that can be treated herein are those "susceptible to amelioration by inhibition of PDE7," which is a property shown by the compounds of the invention. In the case of asthma, for example, claim 19 is directed to its treatment, to the extent that asthma is susceptible to amelioration by inhibition of PDE7.

Moreover, there is considerable literature indicating that compounds that inhibit PDE7 are useful for the treatment of the pathological conditions recited in the claims. For example, A. Nakata et al., *Clinical and Experimental Immunology* 128:460-466 (2002) ("*Nakata*") indicates that "[i[t is significant that T-2585 [PDE7 inhibitor] . . . effectively suppressed IL-5 production by PBMC because accumulating evidence suggests that IL-5 is the key cytokine involved in allergic diseases, such as asthma and atopic dermatitis, associated with eosinophilic inflammation" and that selective inhibitors of PDE7 "are promising drugs for the management of chronic allergic disorders." *Nakata* at page 465. *Nakata*, as well as all other references and patents cited herein, are being submitted in an Information Disclosure Statement filed concurrently with this response. *Nakata* further discusses how PDE7 inhibitors potentially affect immunological diseases, stating that "PDE7 has the potential to regulate human T cell functions including cytokine production, proliferation and expression of activation markers" which "suggests the possible management of various immunological diseases by treatment with selective PDE7 inhibitors." *Id.*

Smith, S. et al. *AJP Lung Cell Molecular Physiology* 284: 279-289 (2003) ("*Smith*") further suggests that inhibition of PDE7 has an active role in treating inflammation. *Smith* states that "PDE7A1 has been identified in cells thought to be central to the pathogenesis of asthma and COPD . . . [and] may suppress a myriad of proinflammatory responses similar to those effected by PDE4 inhibitors such as rolipram." *Smith* at page 287.

Martinez A. et al. *Journal of Medical Chemistry* 43(4): 683-689 (2000) ("Martinez") also discusses studies regarding specific PDE7 inhibitors that can be used for the treatment for T-cell dependent disorders, stating that:

> The biological data reveal that these novel compounds represent the first heterocyclic family of compounds with PDE 7 inhibitory properties appearing to be a new objective for the treatment of T-cell-dependent disorders.

Martinez at page 685.

Moreover, *the state of the art*, as indicated by US patents filed before the present application was filed, demonstrates that one of ordinary skill in the art would have reasonably expected that PDE7 inhibitors could be used for the treatment of the diseases recited in instant claim 19. For example, claims 17 and 19 of U.S. Patent No. 7,122,565, filed on October 1, 2001, recites:

Claim 17:

> A method for treating a disease for which treatment by a **PDE7** inhibitor is indicated, comprising administering to a mammal in need thereof, an effective amount of compound of Formula I of any one of claims 1 to 9, 10, 11, 12 or 13.

Claim 19:

> A method claim 17, in which the disease being treated is selected from visceral pain, inflammatory bowel disease, osteoarthritis, **multiple sclerosis, chronic obstructive pulmonary disease (COPD), asthma, cancer**, acquired immune deficiency syndrome (AIDS), and **graft rejection**.

In addition, claims 16 and 18 of U.S. Patent No. 6,753,340, filed on March 27, 2003, recites:

Claim 16:

> A method of treating a disease which is treatable by inhibition of **PDE7** in a mammal, said method comprising

> administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutical composition comprising a compound of claim 1 and one or more pharmaceutically acceptable excipients or carriers.

Claim 18:

> A method of claim 16 in which the disease to be treated is visceral pain, inflammatory bowel disease, osteoarthritis, **multiple sclerosis**, osteoporosis, **chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer,** acquired immune deficiency syndrome (AIDS) or **graft rejection**.

Moreover, claims 3 and 4 of U.S. Patent No. 6,884,800, filed May 9, 2002, recites:

Claim 3:

> A method for the inhibition of **phosphodiesterase VII**, comprising administering a compound of claim 1 to a host in need thereof.

Claim 4:

> A method for treating an allergic disease, **asthma**, chronic bronchitis, **atopical dermatitis, psoriasis**, a skin disease, an inflammatory disease, **an autoimmune disease, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, ulcerative colitis**, osteoporosis, **transplant rejection reactions**, cachexia, tumour growth, tumour metastases, sepsis, a memory disorder, atherosclerosis or AIDS, comprising administering a compound of claim 1 to a host in need thereof.

Lastly, claims 3 and 4 of U.S. Patent No. 6,531,498, filed May 3, 2002, recites:

Claim 3:

> A method of treating an allergic disorder, **asthma**, chronic bronchitis, **atopic dermatitis, psoriasis**, a skin disorder other than psoriasis, an inflammatory disorder, an **autoimmune disease, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, ulcerative colitis**, osteoporosis, **a transplant rejection reaction**,

cachexia, a tumor growth or a tumor metastases, sepsis, a memory disturbance, atherosclerosis or AIDS comprising administering an effective amount of a pharmaceutical composition of claim 2 to a patient in need thereof.

Claim 4:

A method of inhibiting **phosphodiesterase VII** comprising administering an effective amount of a pharmaceutical composition of claim 2 to a patient in need thereof.

As can be seen from the foregoing review, the teachings of the state of the art at the time the application was filed, comprising the journal articles and issued patents cited above, enable one of ordinary skill in the art to practice the subject matter of claim 19. Accordingly, Applicants respectfully request that this rejection be withdrawn.

IV. Conclusion

Applicants respectfully request that this Amendment be entered by the Examiner, placing claims 1-12, 14 and 19-22 in condition for allowance. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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